Fruit, vegetables, and olive oil and risk of coronary heart disease in Italian women: the EPICOR Study[1–3]

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ABSTRACT

Background: Many observational studies support the recommendation to eat sufficient amounts of fruit and vegetables as part of a healthy diet.

Objective: The present study aimed to investigate the association between consumption of fruit, vegetables, and olive oil and the incidence of coronary heart disease (CHD) in 29,689 women enrolled between 1993 and 1998 in 5 European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts in northern (Turin and Varese), central (Florence), and southern (Naples and Ragusa) Italy.

Design: Baseline dietary, anthropometric, and lifestyle characteristics were collected. Major events of CHD (fatal and nonfatal myocardial infarction and coronary revascularization) were identified through a review of clinical records. Analyses were stratified by center and adjusted for hypertension, smoking, education, menopause, physical activity, anthropometric measures, nonalcohol energy, alcohol, total meat, vegetables in analyses for fruit, and fruit in analyses for vegetables.

Results: During a mean follow-up of 7.85 y, 144 major CHD events were identified. A strong reduction in CHD risk among women in the highest quartile of consumption of leafy vegetables (hazard ratio: 0.54; 95% CI: 0.33, 0.90; *P* for trend = 0.03) and olive oil (hazard ratio: 0.56; 95% CI: 0.31, 0.99; *P* for trend = 0.04) was found. In contrast, no association emerged between fruit consumption and CHD risk.

Conclusion: An inverse association between increasing consumption of leafy vegetables and olive oil and CHD risk emerged in this large cohort of Italian women. *Am J Clin Nutr* 2011;93:275–83.

INTRODUCTION

According to World Health Statistics for 2006, cardiovascular diseases are responsible for 30% of all deaths globally and for 10% of the global burden of disease (1).

A great number of observational cohort studies support current recommendations to eat sufficient amounts of fruit and vegetables as part of a healthy diet. Fruit and vegetables may indeed reduce chronic diseases and more specifically coronary artery disease (CHD), by means of specific protective constituents, such as fiber, potassium, and several compounds with antioxidant properties (2–4).

In addition, olive oil has been widely studied for its inverse association with CHD, specifically for its favorable effects on the inhibition of oxidative stress, on plasma concentrations of LDL and cholesterol, and on blood pressure (5, 6).

Differences between the 2 sexes are quite evident, and the incidence of CHD is 3 to 4 times higher in men than in women (7). Moreover, the incidence of CHD before the age of 50 y is much lower in women, whereas, after that age, it progressively approaches the incidence in men (8). In their review, Price and Fowkes (7) examined the hypothesis that the sex differential in CHD incidence may result from differences in the prevalence of, or in the susceptibility to, several risk factors related to lifestyle habits, such as smoking status, hypertension, total serum cholesterol, abdominal fat, and diabetes. In females, the occurrence of CHD is also influenced by the sex hormone pattern (9).

Taking into account this complex scenario, the purpose of the present study is to investigate the association between consumption of fruit, vegetables, and olive oil and the incidence of CHD in a large cohort of adult women from 5 Italian areas located in northern, central, and southern Italy.

SUBJECTS AND METHODS

The EPICOR Study is a collaborative prospective investigation that aims to estimate the risk of cardiovascular diseases associated with dietary and lifestyle habits in the Italian cohort of the European Prospective Investigation into Cancer and Nutrition

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(EPIC) Study (10, 11). The 5 Italian centers of the EPIC Study are located in Turin and Varese (northern Italy), Florence (central Italy), and Naples and Ragusa (southern Italy).

A large series of healthy adults were enrolled to identify all newly diagnosed cases of cancer and other relevant chronic diseases occurring after the date of enrollment and to study the risks associated with dietary and lifestyle habits reported at baseline. The participants were contacted by media advertising, among women invited to cancer screening programs, among employees of local companies, and through nonprofit organizations such as blood donors, consumer groups, and cancer aid associations (11). All volunteers signed an informed consent form for the use of their individual clinical data for future research projects. The study protocol was approved by ethics committees centrally at the International Agency for Research on Cancer (Lyon, France) and in Florence for the Italian cohorts.

Baseline measurements

Sociodemographic characteristics such as sex, age, and place of residence were collected. The participants were also requested to give a blood sample.

Lifestyle

The EPIC lifestyle questionnaire was used to assess marital status, smoking habits, educational level, physical activity, reproductive history, and menopausal status and to identify several diseases preceding enrollment including myocardial infarction, stroke, hypertension, hyperlipidemia, and diabetes.

Dietary information

Dietary information was collected with a food-frequency questionnaire (FFQ) specifically developed for the Italian dietary habits and was tested in a pilot phase (12). To capture local dietary behaviors, 2 slightly different versions were developed and used in Naples and Ragusa. A detailed description of the EPIC-Italy FFQ was previously reported (13). Briefly, the questionnaire for north-central Italy was a semiquantitative instrument that was self-administered and checked by trained personnel after compilation. It contains 248 questions concerning 188 different food items. The volunteers were requested to indicate the number of times a given food item was consumed (per day, week, month, or year), from which the absolute frequency of consumption of each item is assessed. The quantity of food consumed was assessed through the selection of an image of a food portion or by the selection of a predefined standard portion when no image was available. For sauces, meat, fish, and vegetables, there were questions on cooking method and type of fat used for preparation and cooking. For tomatoes and other types of fruit and vegetables, the consumption of which, in Italy, is strongly dependent on season, intake was assessed separately in and out of the main cropping season. The questionnaire for Ragusa (438 questions about 217 food items) was developed in a manner similar to that used for the questionnaire for north-central Italy and was administered by trained interviewers. The questionnaire for Naples (154 questions about 140 food items) was a semiquantitative instrument also administered by trained interviewers (14).

Dietary information obtained by the questionnaire was checked, coded, computerized by optical reading, and then transformed into estimates of daily intake of energy (kcal) and 40 nutrients according to Italian food-composition database specifically developed for epidemiologic studies (15).

Anthropometric measures

Anthropometric measurements (weight, height, and waist and hip circumferences) were collected by trained nurses following standard procedures (11, 16).

Blood pressure

Systolic and diastolic blood pressure measurements were conducted by specifically trained operators with the use of a mercury sphygmomanometer following standardized procedures (11). Subjects with a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg (17) or reporting a clinical diagnosis of hypertension and receiving any antihypertensive treatment at baseline were considered hypertensive.

Diabetes and hyperlipidemia

Participants reporting a history of treatment of diabetes or hyperlipidemia at baseline were considered to be diabetic or hyperlipidemic, respectively.

Major CHD ascertainment and verification

The EPIC-Italy Study was based on the enrollment of healthy volunteers. Specific information on previous major diseases, including cardio- and cerebrovascular diseases was collected through the EPIC lifestyle questionnaire. This baseline information, together with additional information obtained through medical record linkages, allowed us to identify and exclude prevalent cases of major coronary and cerebrovascular events.

Outcome definition

In this study we considered only major CHD incident cases (fatal and nonfatal events of myocardial infarction, coronary revascularization, or both) and cases of sudden death for unspecified cardiac event.

After a vital status update, the death certificates were obtained from the Mortality Registries. Suspected CHD deaths were identified when ICD X I20-I25, R96, and R99 codes were reported as the main cause of death and also when E10-E14, I10-I13, I30, I31, I33-I38, I40, I42, I44-I51, I70-I74, and I77 codes were reported together with I20-I25 as associated conditions. Fatal CHD was assigned after evaluation of all the codes reported on the death certificates and verification against hospital discharge and clinical records.

After linkage with the hospital discharge files, all records reporting ICD IX-CM 410–414 codes and/or procedure codes for percutaneous transluminal coronary angioplasty or coronary artery bypass surgery were detected and clinical data were retrieved.

The disease was considered verified when acute myocardial infarction, acute coronary syndrome, or coronary revascularization were noted on the records, backed up by information on symptoms at onset, concentrations of cardiac enzymes and troponins, and electrocardiogram data coded according to the Minnesota Code (18).

Repeated hospital admissions for CHD within 28 d were considered as one event. A cross-check with mortality data was performed, and a nonfatal case was defined when the subject was still alive after 28 d from the CHD diagnosis. Cases were censored at the date of the first event. The end of follow-up was 31 December 2003 in Florence and Naples, 1 January 2002 in Varese, 31 December 2002 in Ragusa, and 31 December 2004 in Turin.

Statistical analysis

In the frame of the EPIC Study, 32,578 women aged 35–74 y were recruited in the 5 Italian cohorts (9526 in Varese, 4557 in Turin, 10,083 in Florence, 3350 in Ragusa, and 5062 in Naples). Women who reported a previous diagnosis of stroke or myocardial infarction at recruitment ($n = 434$), who did not complete the dietary or lifestyle questionnaires ($n = 948$), and who were being treated for hyperlipidemia ($n = 842$) and diabetes ($n = 286$) were excluded. The subjects whose ratio of total energy intake to basal metabolic rate was at the extremes of the distribution (first and last half percentiles) were also excluded. Some women met more than one exclusion criteria.

After all these exclusions, 29,689 women (15,860 premenopausal and 13,829 postmenopausal at recruitment) remained for analysis. The baseline distribution of daily fruit, vegetable, and olive oil consumption and of the main cardiovascular disease risk factors was described according to quartiles of total consumption of vegetables. Continuous variables were reported as energy-adjusted means (± SE) and were compared by using analysis of variance. Categorical variables were expressed as percentages and analyzed by chi-square test.

Energy-adjusted Pearson's correlation coefficients were calculated between olive oil and vegetable consumption and between fruit and vegetable consumption. Person time of follow-up for each participant was computed from the age at enrollment to the age of occurrence of the first major event, end of follow-up, emigration, or death, whichever came first.

Cox proportional hazard models were performed to assess the association of consumption of several types of fruit and vegetables and of olive oil with CHD risk. Analyses were stratified by EPIC center. The analyses for fruit, vegetable, and olive oil intakes were performed by using 2 models: a crude model (including only a term for caloric intake) and an adjusted model.

Fruit, vegetable, and olive oil variables were added in the crude and adjusted models as dummy variables for quartiles of consumption (lowest quartile as reference). Trend tests were performed with the inclusion of each dietary variable ordered as quartiles in the Cox model.

The adjusted models were also performed considering consumption of fruit and vegetables as continuous variables: 100-g increments for total vegetable consumption, 150-g increments for total fruit consumption, 10-g increments for cabbage and olive oil consumption, and 50-g increments for consumption of all other fruit and vegetables.

The following variables were used for the adjustment: education (4 categories: none/elementary school, secondary/professional school, high school, and university degree), smoking status (dummy variables: smokers up to one pack per day, smokers of more than one pack per day, ex-smokers, and never smokers as the reference category), alcohol consumption (dummy variables: nondrinkers; drinkers, more than one drink per day; and drinkers up to one drink per day as the reference category, where 1 drink ≤12 g alcohol/d), body height (cm), body weight (kg), waist circumference (cm), daily no-alcohol caloric intake (log kcal), hypertension (yes or no), menopausal status (pre- and postmenopausal), total physical activity index (4 classes: inactive, moderately inactive, moderately active, and active), and total meat consumption. An additional adjustment for total fruit or total vegetable consumption was also performed in models evaluating the effect of vegetables (overall and by specific subtypes) or fruit (overall and by specific subtypes), respectively.

Further analyses included dummy variables for quartiles of consumption of olive oil in the models. Analyses were also performed separately in pre- and postmenopausal women and after exclusion of women who reported to be "on a diet" for the purpose of losing weight or for health reasons. All analyses were performed with STATA 9 software (StataCorp, College Station, TX).

RESULTS

Overall, 29,689 women (46.6% postmenopausal) were available for analyses after the exclusions. At enrollment, the mean (±SE) age was 50.0 ± 7.9 y (age range: 35–74 y), body weight was 64.5 ± 11.0 kg), body height was 158.6 ± 6.1 cm, daily consumption of total vegetables was 188.7 ± 99.9 g, daily consumption of total fruit was 351.8 ± 207.8 g, and daily olive oil consumption was 24.7 ± 13.0 g.

During an average follow-up of 7.85 y (233,106.6 person-years), 144 major CHD events were identified (104 nonfatal myocardial infarctions, 27 coronary revascularizations, 3 fatal myocardial infarctions with hospitalization, 9 fatal myocardial infarctions without hospitalization, and 1 sudden death for unspecified cardiac events). Thirty-one of 144 events occurred among the 15,860 premenopausal women and 113 among the 13,829 postmenopausal women ($P < 0.0001$).

The baseline characteristics of women according to quartile of total vegetable intake are shown in **Table 1**; the mean (± SE) intake ranged from 86.2 ± 0.5 g/d in the lowest to 321.6 ± 0.5 g/d in the highest quartile. The mean total fruit intake ranged from 319.3 ± 2.4 g/d in the lowest to 392.8 ± 2.4 g/d in the highest quartile of total vegetable intake. Compared with women in the lowest quartile of total vegetable intake, women in the highest quartile were more educated, were more active, had a slightly higher waist circumference and body weight, and had a greater percentage who drank less than one drink per day and were former or current smokers. No differences emerged in the percentage of hypertensive subjects and in mean height across quartiles.

Olive oil consumption was strongly correlated with consumption of total and selected vegetables. In particular, the energy-adjusted Pearson correlation coefficient with olive oil was 0.62 for total vegetables, 0.52 for raw tomatoes, 0.46 for root vegetables, and 0.45 for leafy vegetables (all P values < 0.0001). Only cooked tomatoes (mostly tomato sauce) showed an inverse correlation with olive oil (Pearson correlation coefficient =

TABLE 1

Baseline distribution of fruit and vegetable consumption and main cardiovascular disease risk determinants at enrollment by quartile of total vegetable consumption in 29,689 women in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study–Italy[1]

	Quartile of total vegetable consumption				
	1 (86.2 ± 0.5 g/d)	2 (145.1 ± 0.5 g/d)	3 (202.4 ± 0.5 g/d)	4 (321.6 ± 0.5 g/d)	P^2
Total fruit (g/d)	319.3 ± 2.4	340.1 ± 2.3	355.2 ± 2.3	392.8 ± 2.4	<0.0001
Fruit and vegetables (g/d)	405.5 ± 2.5	485.2 ± 2.4	557.7 ± 2.4	714.5 ± 2.5	<0.0001
Olive oil (g/d)	16.8 ± 0.1	21.6 ± 0.1	25.6 ± 0.1	35.0 ± 0.1	<0.0001
Total meat (g/d)	96.8 ± 0.6	99.5 ± 0.5	98.6 ± 0.5	95.6 ± 0.6	<0.0001
Total energy (kcal/d)[3]	1886.2 ± 533.1	2093.2 ± 541.0	2254.6 ± 567.8	2506.1 ± 635.6	<0.0001
Height (cm)	158.5 ± 0.07	158.6 ± 0.07	158.6 ± 0.07	158.6 ± 0.07	0.5439
Body weight (kg)	63.0 ± 0.1	64.0 ± 0.1	65.0 ± 0.1	66.1 ± 0.1	<0.0001
BMI (kg/m^2)	25.1 ± 0.05	25.5 ± 0.05	25.8 ± 0.05	26.3 ± 0.05	<0.0001
Waist circumference (cm)	79.0 ± 0.1	79.5 ± 0.1	80.4 ± 0.1	81.3 ± 0.1	<0.0001
Postmenopausal (%)	49.7	47.3	44.8	44.5	<0.0001
Hypertension (%)[4]	36.2	35.2	35.3	36.8	0.1441
Physical activity index (%)					<0.0001
Inactive	20.6	20.6	21.3	19.3	
Moderately inactive	31.4	30.2	31.8	31.9	
Moderately active	43.1	43.5	41.3	42.0	
Active	5.0	5.7	5.7	6.8	
Education (%)					<0.0001
None/elementary school	34.1	30.6	27.3	24.7	
Secondary/professional school	33.4	33.7	34.4	34.4	
High school	20.3	22.9	24.6	25.3	
University degree	12.2	12.8	13.8	15.6	
Smoking history (%)					<0.0001
Never smoker	58.3	54.8	51.9	49.2	
Former smoker	17.1	19.4	20.8	23.4	
Current smoker, low	18.6	19.4	19.9	19.4	
Current smoker, high	6.0	6.5	7.3	7.9	
Alcohol consumption (%)					<0.0001
None	19.1	16.2	15.7	16.8	
≤12 g/d	59.0	60.0	60.9	61.0	
>12 g/d	22.0	23.8	23.4	22.2	

[1] Values are energy-adjusted means ± SEs for continuous variables and percentages for categorical variables.
[2] *P* values for continuous variables calculated with a general linear model and calculated for categorical variables with a chi-square test.
[3] Includes energy from alcohol.
[4] Defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or a clinical diagnosis of hypertension and antihypertensive treatment at baseline.

−0.08, *P* value < 0.0001). Overall, a low but significant correlation between fruit and vegetable consumption was observed (Pearson correlation coefficient = 0.15, *P* value < 0.0001; data not shown).

A significant inverse association between leafy vegetable consumption and CHD risk emerged in the adjusted model (*P* for trend = 0.03), with a 50% reduction for women in the highest quartile of consumption in comparison with women in the lowest quartile (HR: 0.54; 95% CI: 0.33, 0.90) (**Table 2**). An inverse association between increasing consumption of raw leafy vegetables and the risk of CHD was suggested (*P* for trend = 0.06). A protective association of olive oil also emerged (*P* for trend = 0.03 and 0.04 in the crude and adjusted models, respectively). On the other hand, no significant association between increasing consumption of total fruit and CHD risk emerged.

The separate adjusted models with continuous increments of consumption suggested an inverse association with CHD risk of both leafy vegetables (*P* = 0.06) and olive oil (*P* = 0.07) (data not shown). In additional models with mutual adjustment for olive oil and different types of vegetables, the point estimates no longer showed a significant association between the consumption of total leafy vegetables and CHD risk (HR for quartile 4 compared with quartile 1: 0.64; *P* value = 0.11).

No modification effect of menopausal status emerged. In the stratum of postmenopausal women, inverse associations emerged between leafy vegetable consumption and CHD risk (HR for quartile 4 compared with quartile 1: 0.46; 95% CI: 0.27, 0.81; *P* for trend = 0.03) and between raw leafy vegetable consumption and CHD risk (HR for quartile 4 compared with quartile 1: 0.54; 95% CI: 0.31, 0.95; *P* for trend = 0.03). An inverse association between olive oil consumption and CHD risk also emerged in the stratum of postmenopausal women (**Table 3**). In the stratum of premenopausal women, no clear effects of vegetables and olive oil consumption emerged. The results did not change materially after the exclusion of 4592 women who, at enrollment, reported following a specific diet to lose weight or for health reasons.

TABLE 2
Hazard ratios (HRs) of coronary heart disease (with 95% CIs and *P* values for trend) according to quartile of fruit, vegetable, and olive oil consumption in 29,689 women in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study–Italy

	Intake cutoffs	Cases	Crude HR[1]	95% CI	*P* for trend	Adjusted HR[2]	95% CI	*P* for trend
	g/d	*n*						
Total vegetables[3]								
Quartile 1	≤117.5	45	1.00	—		1.00	—	
Quartile 2	≤171.5	27	0.56	(0.34, 0.91)		0.54	(0.34, 0.90)	
Quartile 3	≤241.7	36	0.69	(0.43, 1.12)		0.68	(0.42, 1.10)	
Quartile 4	>241.7	36	0.67	(0.40, 1.11)	0.20	0.62	(0.37, 1.04)	0.13
Leafy vegetables								
Quartile 1	≤17.6	43	1.00	—		1.00	—	
Quartile 2	≤30.6	32	0.69	(0.43, 1.10)		0.64	(0.40, 1.03)	
Quartile 3	≤50.8	39	0.75	(0.48, 1.19)		0.71	(0.45, 1.12)	
Quartile 4	>50.8	30	0.6	(0.37, 0.98)	0.07	0.54	(0.33, 0.90)	0.03
Leafy vegetables (cooked)								
Quartile 1	≤6.2	37	1.00	—		1.00	—	
Quartile 2	≤12.0	35	0.96	(0.60, 1.53)		0.98	(0.61, 1.56)	
Quartile 3	≤22.9	35	0.88	(0.54, 1.43)		0.85	(0.52, 1.39)	
Quartile 4	>22.9	37	0.79	(0.47, 1.33)	0.36	0.76	(0.45, 1.29)	0.28
Leafy vegetables (raw)								
Quartile 1	≤6.7	40	1.00	—		1.00	—	
Quartile 2	≤14.3	39	0.83	(0.53, 1.30)		0.82	(0.52, 1.28)	
Quartile 3	≤28.7	37	0.80	(0.51, 1.27)		0.79	(0.50, 1.26)	
Quartile 4	>28.7	28	0.65	(0.40, 1.07)	0.10	0.61	(0.37, 1.01)	0.06
Tomatoes (raw)								
Quartile 1	≤17.2	45	1.00	—		1.00	—	
Quartile 2	≤37.1	36	0.85	(0.54, 1.34)		0.91	(0.58, 1.42)	
Quartile 3	≤66.6	34	0.83	(0.52, 1.33)		0.83	(0.52, 1.34)	
Quartile 4	>66.6	29	0.80	(0.48, 1.33)	0.38	0.80	(0.47, 1.34)	0.35
Tomatoes (cooked)								
Quartile 1	≤5.4	33	1.00	—		1.00	—	
Quartile 2	≤12.5	38	1.25	(0.78, 2.00)		1.28	(0.79, 2.06)	
Quartile 3	≤24.9	33	1.10	(0.67, 1.81)		1.15	(0.69, 1.92)	
Quartile 4	>24.9	40	1.20	(0.72, 2.01)	0.62	1.20	(0.70, 2.08)	0.61
Root vegetables								
Quartile 1	≤3.2	38	1.00	—		1.00	—	
Quartile 2	≤8.6	32	0.69	(0.43, 1.11)		0.80	(0.50, 1.30)	
Quartile 3	≤21.4	34	0.88	(0.55, 1.42)		1.08	(0.67, 1.75)	
Quartile 4	>21.4	40	1.14	(0.72, 1.81)	0.46	1.41	(0.87, 2.28)	0.12
Cabbages								
Quartile 1	≤1.2	38	1.00	—		1.00	—	
Quartile 2	≤3.7	39	1.17	(0.75, 1.84)		1.24	(0.79, 1.95)	
Quartile 3	≤8.2	34	0.86	(0.53, 1.38)		0.90	(0.56, 1.46)	
Quartile 4	>8.2	33	0.89	(0.54, 1.45)	0.43	0.88	(0.53, 1.45)	0.42
Other vegetables								
Quartile 1	≤17.4	41	1.00	—		1.00	—	
Quartile 2	≤30.5	25	0.61	(0.37, 1.01)		0.62	(0.37, 1.02)	
Quartile 3	≤50.0	38	0.88	(0.55, 1.39)		0.86	(0.54, 1.38)	
Quartile 4	>50.0	40	0.79	(0.47, 1.32)	0.59	0.76	(0.44, 1.29)	0.49
Total fruit								
Quartile 1	≤219.3	31	1.00	—		1.00	—	
Quartile 2	≤318.6	37	1.12	(0.69, 1.81)		1.36	(0.84, 1.93)	
Quartile 3	≤441.3	43	1.32	(0.83, 2.12)		1.68	(1.04, 2.72)	
Quartile 4	>441.3	33	0.96	(0.57, 1.61)	0.95	1.24	(0.73, 2.12)	0.28
Citrus fruit								
Quartile 1	≤37.5	32	1.00	—		1.00	—	
Quartile 2	≤68.8	40	0.33	(0.84, 2.13)		1.52	(0.95, 2.42)	
Quartile 3	≤110.4	39	1.20	(0.74, 1.92)		1.31	(0.81, 2.11)	
Quartile 4	>110.4	33	1.24	(0.75, 2.05)	0.51	1.47	(0.89, 2.44)	0.21
Noncitrus fruit								
Quartile 1	≤160.3	26	1.00	—		1.00	—	
Quartile 2	≤244.7	47	1.66	(1.02, 2.68)		2.03	(1.25, 3.32)	
Quartile 3	≤338.5	37	1.35	(0.82, 2.25)		1.72	(1.03, 2.89)	
Quartile 4	>338.5	34	1.07	(0.65, 1.83)	0.84	1.43	(0.82, 2.48)	0.38

(Continued)

TABLE 2 (*Continued*)

	Intake cutoffs	Cases	Crude HR[1]	95% CI	*P* for trend	Adjusted HR[2]	95% CI	*P* for trend
	g/d	*n*						
Fruit and vegetables								
Quartile 1	≤372.0	36	1.00	—		1.00	—	
Quartile 2	≤504.5	35	0.95	(0.59, 1.52)		1.04	(0.65, 1.68)	
Quartile 3	≤663.4	36	0.94	(0.58, 1.52)		1.08	(0.66, 1.77)	
Quartile 4	>663.4	37	0.92	(0.55, 1.53)	0.75	1.10	(0.65, 1.87)	0.71
Olive oil								
Quartile 1	≤15.9	45	1.00	—		1.00	—	
Quartile 2	≤22.5	46	1.06	(0.70, 1.61)		1.06	(0.70, 1.61)	
Quartile 3	≤31.2	32	0.77	(0.49, 1.25)		0.81	(0.50, 1.30)	
Quartile 4	>31.2	21	0.54	(0.31, 0.95)	0.03	0.56	(0.31, 0.99)	0.04

[1] Adjusted for energy intake (log kcal).

[2] Adjusted for educational level (4 classes: none or elementary school, secondary or professional school, high school, and degree), smoking status (dummy variables: smokers, to one pack per day; smokers, more than one pack per day; and ex-smokers with nonsmokers as the reference category), alcohol consumption (dummy variables: nondrinkers and drinkers, more than one drink per day with drinkers to one drink per day as the reference category), body height (cm), body weight (kg), waist circumference (cm), daily nonalcohol caloric intake (log kcal), hypertension (yes or no), menopausal status, total physical activity index (4 classes: inactive, moderately inactive, moderately active, and active), total meat consumption (50-g increments), vegetable consumption (50-g increments) in analyses for fruit, and fruit consumption (50-g increments) in analyses for vegetables.

[3] Leafy vegetables, tomatoes, root vegetables, cabbages, onion, garlic, mixed salad, and other vegetables (eg, fruiting vegetables, artichokes, celery, and fennel).

DISCUSSION

This study, to our knowledge, is the first prospective study to examine the association between fruit, vegetable, and olive oil consumption and the risk of CHD in a large cohort of healthy adult Italian women. We found that an increasing consumption of leafy vegetables was associated with a reduced CHD risk among middle-aged women without a diagnosis of stroke, myocardial infarction, diabetes, or hyperlipidemia at recruitment. An inverse association of increasing olive oil consumption with CHD risk also emerged.

The association between consumption of fruit and vegetables and CHD in middle-aged women was investigated in 2 American observational cohort studies (19, 20). In the Nurses' Health Study (19) (1127 cases of nonfatal myocardial infarction or fatal CHD among 84,251 US women 34–59 y of age without cancer, diabetes, or cardiovascular disease at baseline), an inverse association between the consumption of fruit and vegetable consumption and CHD risk was evident, particularly for green leafy vegetables and vitamin C rich fruit and vegetables.

In the Women's Health Study (20) (126 cases of myocardial infarction among 39,127 US women with a mean age of 54 y without heart disease, stroke, or cancer at baseline), the results suggested an inverse, although not significant, association between higher intakes of fruit and vegetables and cardiovascular diseases. These 2 studies are substantially in agreement with our results of an inverse association of a high consumption of vegetables with CHD risk.

It has been shown that dietary patterns rich in plant foods and low in animal fats are associated with a reduced risk of CHD (21–25). In our study, the risk reduction associated with increasing intakes of leafy vegetables, in the model also adjusted for total meat consumption, could be attributable not only to the amount of vegetables consumed but also to the general composition of the diet and in particular to the relation between plant origin foods and animal origin foods. In our subjects, the energy-adjusted mean daily total meat consumption significantly decreased, from a mean (±SE) of 99.5 ± 0.5 g/d in the second quartile to 95.6 ± 0.6 g/d in the fourth quartile of total vegetable consumption (Table 1).

The positive, although nonsignificant, association between fruit consumption and CHD risk that emerged in our cohort could be partially explained by considerations about food availability and eating habits typical of the Italian population. Whereas in the United States and northern European countries, a high intake of fruit tends to be associated with a prudent diet pattern (3, 26), in Italy, fruit consumption is widespread and deeply rooted in the daily habits of the general population, including individuals with unhealthy dietary patterns (13, 27). Moreover, in Italy, fruit is readily available and varied, and retail prices are relatively low in comparison with other countries (28). In our cohort we observed a low correlation between total fruit and vegetable consumption; indeed, slight variation was observed in the mean daily consumption of fruit across quartiles of vegetables.

Many mechanisms are likely responsible for the protective effect of plant-origin foods on cardiovascular diseases. For example, micronutrients—such as folate, antioxidant vitamins, and potassium, which are particularly high in green leafy vegetables—have a supposed beneficial effect (2, 29). Folate, alone or in combination with vitamin B-6 and vitamin B-12, reduces blood homocysteine concentrations (19, 30), and it was shown that hyperhomocysteinemia is a significant and independent risk factor for cardiovascular diseases, despite the not yet clear underlying mechanism (31). Several epidemiologic studies have reported that vitamins C, E, and β-carotene from the diet or supplements are associated with a lower risk of CHD (32–34). A diet rich in vegetables and fruit, and therefore rich in antioxidant vitamins, can significantly increase the antioxidant capacity of serum and protect against lipid peroxidation and consequently against the pathogenesis of atherosclerosis (35). Potassium has been shown to be inversely associated with blood pressure values in cross-sectional studies (36, 37) and thereby indirectly contributes to the reduction in cardiovascular risk.

TABLE 3
Hazard ratios (HRs) of coronary heart disease (with 95% CIs and *P* values for trend) according to quartile of fruit, vegetable, and olive oil consumption in 13,829 postmenopausal women in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study–Italy

	Intake cutoffs	Cases	Adjusted HR[1]	95% CI	*P* for trend
	g/d	*n*			
Total vegetables[2]					
Quartile 1	≤117.5	36	1.00	—	
Quartile 2	≤171.5	22	0.56	(0.33, 0.97)	
Quartile 3	≤241.7	28	0.67	(0.39, 1.14)	
Quartile 4	>241.7	27	0.57	(0.31, 1.02)	0.10
Leafy vegetables					
Quartile 1	≤17.6	38	1.00	—	
Quartile 2	≤30.6	20	0.44	(0.25, 0.77)	
Quartile 3	≤50.8	32	0.66	(0.40, 1.09)	
Quartile 4	>50.8	23	0.46	(0.27, 0.81)	0.03
Leafy vegetables (cooked)					
Quartile 1	≤6.2	37	1.00	—	
Quartile 2	≤12.0	31	1.01	(0.61, 1.67)	
Quartile 3	≤22.9	23	0.63	(0.35, 1.12)	
Quartile 4	>22.9	28	0.66	(0.36, 1.20)	0.09
Leafy vegetables (raw)					
Quartile 1	≤6.7	34	1.00	—	
Quartile 2	≤14.3	30	0.71	(0.43, 1.17)	
Quartile 3	≤28.7	27	0.66	(0.40, 1.11)	
Quartile 4	>28.7	22	0.54	(0.31, 0.95)	0.03
Total fruit					
Quartile 1	≤219.3	22	1.00	—	
Quartile 2	≤318.6	30	1.50	(0.86, 2.62)	
Quartile 3	≤441.1	32	1.70	(0.97, 2.98)	
Quartile 4	>441.1	29	1.45	(0.79, 2.67)	0.21
Olive oil					
Quartile 1	≤15.9	37	1.00	—	
Quartile 2	≤22.5	34	0.94	(0.58, 1.51)	
Quartile 3	≤31.2	24	0.71	(0.42, 1.22)	
Quartile 4	>31.2	18	0.55	(0.29, 1.02)	0.04

[1] Adjusted for educational level (4 classes: none or elementary school, secondary or professional school, high school, and degree), smoking status (dummy variables: smokers, to one pack per day; smokers, more than one pack per day; and ex-smokers with nonsmokers as the reference category), alcohol consumption (dummy variables: nondrinkers and drinkers, more than one drink per day with drinkers to one drink per day as the reference category), body height (cm), body weight (kg), waist circumference (cm), daily nonalcohol caloric intake (log kcal), hypertension (yes or no), menopausal status, total physical activity index (4 classes: inactive, moderately inactive, moderately active, and active), total meat consumption (50-g increments), vegetable consumption (50-g increments) in analyses for fruit, and fruit consumption (50-g increments) in analyses for vegetables.

[2] Leafy vegetables, tomatoes, root vegetables, cabbages, onion, garlic, mixed salad, and other vegetables (eg, fruiting vegetables, artichokes, celery, and fennel).

In our cohort, a risk reduction associated with olive oil consumption was also observed. In Mediterranean countries, olive oil is an important constituent of the typical diet and is considered a major factor in preserving a healthy and relatively disease-free population. In a review Owen et al (6) presented evidence that the antioxidant phenolic fraction, along with high contents of squalene and oleic acid, may confer to olive oil its health-promoting properties. Recent studies and reviews confirmed the effects of olive oil polyphenols on heart disease risk factors and oxidative damage (38–40).

The strong correlation that we observed between olive oil and vegetable consumption in this cohort of Italian women was related to the habit of consuming olive oil as the main dressing fat for vegetables according to the Mediterranean tradition, which makes it difficult to disentangle the effect of olive oil and vegetables. The only exception was the inverse correlation with the consumption of cooked tomatoes. Pasta with tomato sauce is a widely consumed dish and is often associated, in our country, with an unhealthy dietary pattern rich in meat and low in vegetables and olive oil consumption (41). The inclusion in the statistical model of a term for olive oil did non materially change the point estimates, although the results were no longer statistically significant, which supports an independent protective effect of the consumption of leafy vegetables and olive oil.

In our cohort, no effect modification of menopausal status emerged, although a protective effect of leafy vegetables and olive oil was evident only in postmenopausal women. The small number of CHD events probably contributed to the lack associations in premenopausal women.

In a previous study in the EPIC-Florence cohort, Masala et al (37) found an inverse association between increasing consumption of vegetables and systolic and diastolic blood pressure values in women not clinically classified as hypertensive. The flat distribution of hypertensive subjects across quartiles of total vegetable consumption observed in this study may have been due to compliance by the diagnosed hypertensive subjects to the recommended healthy diet rich in fruit and vegetables. In our study, the individuals with high blood pressure values measured at baseline were considered hypertensive, as were individuals with antihypertensive treatment reported at baseline as result of a clinical diagnosis of hypertension.

The strengths of this study were its prospective design and the possibility to assess the dietary habits by using an FFQ specifically designed for Italian dietary habits and thus capable of capturing differences in food consumption. In the frame of EPIC-Italy and to evaluate the accuracy of the dietary information collected, food consumption from FFQ was compared with the results of standardized computer-driven 24-h dietary recall interviews collected from 8% of the EPIC-Italy cohort. The results obtained with the 2 instruments were similar for most of the main food items, which attests to the general high quality of the information obtained by both instruments (13).

It is well known that lifestyle habits other than diet (hypertension, physical inactivity, alcohol drinking, smoking, and waist circumference) are strongly associated with an increased CHD risk (8). We were able to adjust for these factors although a residual confounding effect cannot be excluded. The quite small differences in the results obtained in the crude and adjusted models were probably related to a limited confounding effect of socioeconomic and lifestyle variables in this study population of Italian women, which supports the validity of our results.

In contrast, we had the possibility to identify and exclude from the analyses women with a diagnosis of diabetes or hyperlipidemia at enrollment—a subgroup at increased risk of CHD in which a change toward a more healthy dietary pattern could have already occurred as a consequence of the clinical diagnosis—which possibly resulted in a dilution of the real associations.

Moreover, similar results were obtained from the analyses in which subjects who reported to be "on a diet" at enrollment were excluded, which suggests that reverse causation should not play a relevant role in this study.

A limitation of the study was that data on eating habits were collected with a single dietary assessment that referred to the 12 mo preceding enrollment (to take seasonal variation into account). Some participants may have changed their dietary habits during the follow-up period, which weakened the relative risk estimates.

In conclusion, this study confirms the inverse association between a high consumption of leafy vegetables (salad greens, chard, spinach, and other leafy greens) and olive oil and coronary heart disease in a large cohort of Italian women and provides further evidence in support of recommendations aimed at increasing the consumption of vegetables in a healthy diet.

The authors' responsibilities were as follows—BB and GM: wrote the manuscript and contributed to the analysis and interpretation of the data and to the study conception; DP and GM: conceived the study and provided critical revision of the manuscript for important intellectual content; C Sai, SS, CC, PC, RT, CA, and PV: provided critical revision of the manuscript for important intellectual content; BB, C Sac, SG, GF, and AM: contributed to the collection of data and reviewed the manuscript; and SP: was the study guarantor. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. None of the authors had any personal or financial conflicts of interest.

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